

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for: 040196

Trade Name : WARFARIN SODIUM TABLETS USP

**Generic Name: Warfarin Sodium Tablets USP 1mg, 2mg, 2.5mg,
4mg, 5mg, 7.5mg and 10mg**

Sponsor : Invamed Inc.

Approval Date: September 30, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040196

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040196

APPROVAL LETTER

SEP 30 1997

Invamed Inc.
Attention: Mahendra R. Patel
2400 Route 130
Dayton, NJ 08810
|||||

Dear Sir:

This is in reference to your abbreviated new drug application dated June 14, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Warfarin Sodium Tablets USP, 1 mg, 2 mg, 2.5 mg, 4 mg, 5 mg, 7.5 mg and 10 mg.

Reference is also made to your amendments dated December 20, 1996; and June 27, July 1, August 21, and two amendments dated September 25, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Warfarin Sodium Tablets USP, 1 mg, 2 mg, 2.5 mg, 4 mg, 5 mg, 7.5 mg and 10 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Coumadin® Tablets, 1 mg, 2 mg, 2.5 mg, 4 mg, 5 mg, 7.5 mg and 10 mg, respectively, of Dupont Merck Pharmaceutical Co.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

9/30/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040196

FINAL PRINTED LABELING

NDC 52189-309-24

i invamed inc.

Warfarin Sodium Tablets USP

1 mg

HIGHLY POTENT ANTICOAGULANT

WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.

100 TABLETS

EACH TABLET CONTAINS:

Warfarin Sodium 1 mg

USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

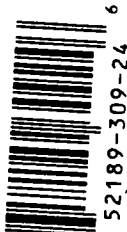
Dispense in a tight, light-resistant container as defined in the USP.

Reseal cap tightly.

CAUTION: Federal law prohibits dispensing without prescription.

Store at controlled room temperature 15° to 30°C (59° to 86°F) and protect from light.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA



N 3

Lot No.:

Exp. Date:

MF # 959A

52189-309-24

NDC 52189-309-30

i invamed inc.

Warfarin Sodium Tablets USP

1 mg

HIGHLY POTENT ANTICOAGULANT

WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.

1000 TABLETS

EACH TABLET CONTAINS:

Warfarin Sodium 1 mg

USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

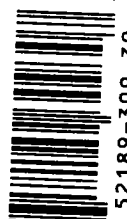
Dispense in a tight, light-resistant container as defined in the USP.

Reseal cap tightly.

CAUTION: Federal law prohibits dispensing without prescription.

Store at controlled room temperature 15° to 30°C (59° to 86°F) and protect from light.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA



N 3

Lot No.:

Exp. Date:

MF # 951A

52189-309-30

NDC 52189-315-24

invamed inc.

**Warfarin Sodium
Tablets USP**

10 mg

HIGHLY POTENT ANTICOAGULANT

WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.

100 TABLETS

EACH TABLET CONTAINS:
Warfarin Sodium 10 mg

USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

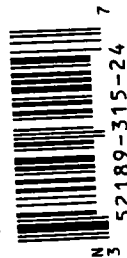
Dispense in a tight, light-resistant container as defined in the USP.

Reseal cap tightly.

CAUTION: Federal law prohibits dispensing without prescription.

Store at controlled room temperature 15° to 30°C (59° to 86°F) and protect from light.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA



Lot No.:
Exp. Date:
MF # 980A

Lot No.
Exp. Dt.
MF # 981

NDC 52189-315-30

invamed inc.

**Warfarin Sodium
Tablets USP**

10 mg

HIGHLY POTENT ANTICOAGULANT

WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.

1000 TABLETS

EACH TABLET CONTAINS:
Warfarin Sodium 10 mg

USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

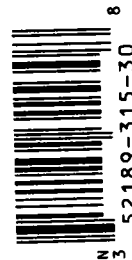
Dispense in a tight, light-resistant container as defined in the USP.

Reseal cap tightly.

CAUTION: Federal law prohibits dispensing without prescription.

Store at controlled room temperature 15° to 30°C (59° to 86°F) and protect from light.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA



Lot No.:
Exp. Date:
MF # 982A

NDC 52189-314-24

i invamed inc.

Warfarin Sodium Tablets USP

7.5 mg

HIGHLY POTENT ANTICOAGULANT

WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.

100 TABLETS

EACH TABLET CONTAINS:

Warfarin Sodium 7.5 mg

USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

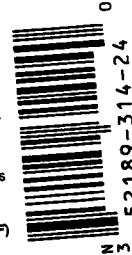
Dispense in a tight, light-resistant container as defined in the USP.

Reseal cap tightly.

CAUTION: Federal law prohibits dispensing without prescription.

Store at controlled room temperature 15° to 30°C (59° to 86°F) and protect from light.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA



Lot No.:
Exp. Date:
MF # 977A

NDC 52189-314-30

i invamed inc.

Warfarin Sodium Tablets USP

7.5 mg

HIGHLY POTENT ANTICOAGULANT

WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.

1000 TABLETS

EACH TABLET CONTAINS:

Warfarin Sodium 7.5 mg

USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

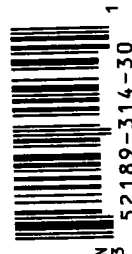
Dispense in a tight, light-resistant container as defined in the USP.

Reseal cap tightly.

CAUTION: Federal law prohibits dispensing without prescription.

Store at controlled room temperature 15° to 30°C (59° to 86°F) and protect from light.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA



Lot No.:
Exp. Date:
MF # 979A

NDC 52189-313-11
invamed_{inc.}
**Warfarin Sodium
Tablets USP**
5 mg

HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdose.
Do not use or dispense before reading directions and
warnings in accompanying product information.

30 TABLETS

EACH TABLET CONTAINS:
Warfarin Sodium 5 mg
USUAL DOSAGE: See accompanying prescribing
information.
Keep this and all drugs out of the reach of children.
Dispense in a tight, light-resistant container as
defined in the USP.
Reseal cap tightly.
CAUTION: Federal law prohibits dispensing without
prescription.
Store at controlled room temperature 15° to 30°C
(59° to 86°F) and protect from light.
Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA



52189-313-11

Lot No.
Exp. Date
MF # 977A

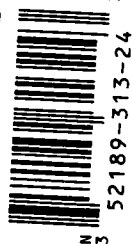
NDC 52189-313-24
invamed_{inc.}
**Warfarin Sodium
Tablets USP**
5 mg

HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from
overdose. Do not use or dispense
before reading directions and warnings in
accompanying product information.

100 TABLETS

EACH TABLET CONTAINS:
Warfarin Sodium 5 mg
USUAL DOSAGE: See accompanying
prescribing information.
Keep this and all drugs out of the reach
of children.
Dispense in a tight, light-resistant
container as defined in the USP.
Reseal cap tightly.
CAUTION: Federal law prohibits
dispensing without prescription.
Store at controlled room
temperature 15° to 30°C (59° to 86°F)
and protect from light.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA



Lot No.:
Exp. Date:
MF # 974A

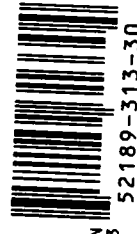
NDC 52189-313-30
invamed_{inc.}
**Warfarin Sodium
Tablets USP**
5 mg

HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from
overdose. Do not use or dispense before
reading directions and warnings in
accompanying product information.

1000 TABLETS

EACH TABLET CONTAINS:
Warfarin Sodium 5 mg
USUAL DOSAGE: See accompanying
prescribing information.
Keep this and all drugs out of the reach
of children.
Dispense in a tight, light-resistant
container as defined in the USP.
Reseal cap tightly.
CAUTION: Federal law prohibits
dispensing without prescription.
Store at controlled room temperature
15° to 30°C (59° to 86°F) and protect
from light.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA



Lot No.:
Exp. Date:
MF # 976A

NDC 52189-312-24

i invamed inc.

Warfarin Sodium Tablets USP

4 mg

HIGHLY POTENT ANTICOAGULANT

WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.

100 TABLETS

EACH TABLET CONTAINS:

Warfarin Sodium 4 mg

USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight, light-resistant container as defined in the USP.

Reseal cap tightly.

CAUTION: Federal law prohibits dispensing without prescription.

Store at controlled room temperature 15° to 30°C (59° to 86°F) and protect from light.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA



52189-312-24

Lot No.:
Exp. Date:
MF # 970A

NDC 52189-312-30

i invamed inc.

Warfarin Sodium Tablets USP

4 mg

HIGHLY POTENT ANTICOAGULANT

WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.

1000 TABLETS

EACH TABLET CONTAINS:

Warfarin Sodium 4 mg

USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight, light-resistant container as defined in the USP.

Reseal cap tightly.

CAUTION: Federal law prohibits dispensing without prescription.

Store at controlled room temperature 15° to 30°C (59° to 86°F) and protect from light.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA



52189-312-30

Lot No.:
Exp. Date:
MF # 972A

NDC 52189-311-11

invamed inc.

**Warfarin Sodium
Tablets USP**

2.5 mg

HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdosage.
Do not use or dispense before reading directions and
warnings in accompanying product information.

30 TABLETS

EACH TABLET CONTAINS:

Warfarin Sodium 2.5 mg

USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight, light-resistant container as defined in the USP.

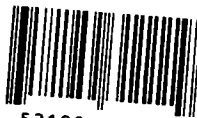
Reseal cap tightly.

CAUTION: Federal law prohibits dispensing without prescription.

Store at controlled room temperature 15° to 30°C

(59° to 86°F) and protect from light.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA



52189-311-11

Lot No.:
Exp. Date:
MF # 966A

NDC 52189-311-24

invamed inc.

**Warfarin Sodium
Tablets USP**

2.5 mg

HIGHLY POTENT ANTICOAGULANT

WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.

100 TABLETS

EACH TABLET CONTAINS:

Warfarin Sodium 2.5 mg

USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

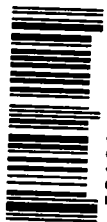
Dispense in a tight, light-resistant container as defined in the USP.

Reseal cap tightly.

CAUTION: Federal law prohibits dispensing without prescription.

Store at controlled room temperature 15° to 30°C (59° to 86°F) and protect from light.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA



52189-311-24

Lot No.:
Exp. Date:
MF # 967A

NDC 52189-311-30

invamed inc.

**Warfarin Sodium
Tablets USP**

2.5 mg

HIGHLY POTENT ANTICOAGULANT

WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.

1000 TABLETS

EACH TABLET CONTAINS:

Warfarin Sodium 2.5 mg

USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight, light-resistant container as defined in the USP.

Reseal cap tightly.

CAUTION: Federal law prohibits dispensing without prescription.

Store at controlled room temperature 15° to 30°C (59° to 86°F) and protect from light.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA



52189-311-30

Lot No.:
Exp. Date:
MF # 968A

NDC 52189-310-11

invamed inc.

**Warfarin Sodium
Tablets USP**

2 mg

HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdosage.
Do not use or dispense before reading directions and
warnings in accompanying product information.

30 TABLETS

EACH TABLET CONTAINS:

Warfarin Sodium 2 mg
USUAL DOSAGE: See accompanying prescribing
information.

Keep this and all drugs out of the reach of children.
Dispense in a tight, light-resistant container as
defined in the USP.

Reseal cap tightly.

CAUTION: Federal law prohibits dispensing without
prescription.

Store at controlled room temperature 15° to 30°C
(59° to 86°F) and protect from light.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA



52189-310-11

Lot No:
Exp. Date:
MF # 963A

NDC 52189-310-24

invamed inc.

**Warfarin Sodium
Tablets USP**

2 mg

HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from
overdosage. Do not use or dispense
before reading directions and warnings in
accompanying product information.

100 TABLETS

EACH TABLET CONTAINS:

Warfarin Sodium 2 mg
USUAL DOSAGE: See accompanying
prescribing information.

Keep this and all drugs out of the reach of children.
Dispense in a tight, light-resistant
container as defined in the USP.

Reseal cap tightly.

CAUTION: Federal law prohibits
dispensing without prescription.

Store at controlled room
temperature 15° to 30°C (59° to 86°F)
and protect from light.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA



52189-310-24

Lot No:
Exp. Date:
MF # 963A

NDC 52189-310-30

invamed inc.

**Warfarin Sodium
Tablets USP**

2 mg

HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from
overdosage. Do not use or dispense before
reading directions and warnings in
accompanying product information.

1000 TABLETS

EACH TABLET CONTAINS:

Warfarin Sodium 2 mg
USUAL DOSAGE: See accompanying
prescribing information.

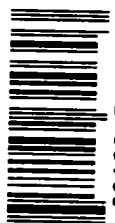
Keep this and all drugs out of the reach of children.
Dispense in a tight, light-resistant
container as defined in the USP.

Reseal cap tightly.

CAUTION: Federal law prohibits
dispensing without prescription.

Store at controlled room temperature
15° to 30°C (59° to 86°F) and protect
from light.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA



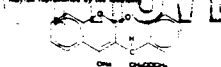
52189-310-30

Lot No:
Exp. Date:
MF # 963A

0 1106135 2

WARFARIN SODIUM TABLETS USP

DESCRIPTION: Crystalline warfarin sodium is a white to light yellow, odorless, crystalline powder. It is soluble in water, slightly soluble in alcohol, and very slightly soluble in chloroform and in ether. Warfarin sodium tablets USP for oral administration are supplied in seven strengths containing 1 mg, 2 mg, 2.5 mg, 4 mg, 5 mg, 7.5 mg, or 10 mg of warfarin sodium. Inactive ingredients:



Molecular Weight 330.32

Crystalline warfarin sodium occurs as a white, odorless crystalline powder, having a slightly bitter taste. It is described by light and is very soluble in water, freely soluble in alcohol, very slightly soluble in chloroform and in ether. Warfarin Sodium Tablets USP for oral administration are supplied in seven strengths containing 1 mg, 2 mg, 2.5 mg, 4 mg, 5 mg, 7.5 mg, or 10 mg of warfarin sodium. Inactive ingredients:

1 mg tablet	corn starch, D&C Red #6 lake color, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and mannitol
2 mg tablet	corn starch, FD&C Blue #2 lake color, FD&C Red #40 lake color, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and mannitol
2.5 mg tablet	corn starch, FD&C Blue #2 lake color, FD&C Yellow #5 lake color, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and mannitol
4 mg tablet	corn starch, FD&C Blue #2 lake color, FD&C Red #2 lake color, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and mannitol
5 mg tablet	corn starch, FD&C Yellow #5 lake color, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and mannitol
7.5 mg tablet	corn starch, FD&C Yellow #5 lake color, FD&C Yellow #10 lake color, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and mannitol
10 mg tablet	corn starch, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and mannitol

CLINICAL PHARMACOLOGY

Warfarin sodium and other warfarin sodium anticoagulants act by inhibiting the synthesis of vitamin K dependent clotting factors, which include Factors II, VII, IX and X, and the anticoagulant proteins C and S. Half-lives of these clotting factors are as follows: Factor II - 60 hours, VII - 4-6 hours, IX - 24 hours, and X - 48-72 hours. The half-lives of proteins C and S are approximately 8 hours and 30 hours, respectively. The resultant of warfarin is a sequential depression of Factors VII, IX, X and II activities. Vitamin K is an essential cofactor for the post-translational synthesis of the vitamin K dependent clotting factors. The vitamin promotes the biosynthesis of γ-carboxyglutamic acid residues in the proteins which are essential for biological activity. Warfarin is thought to interfere with clotting factor synthesis by inhibition of the regeneration of vitamin K, thereby decreasing the degree of expression of dependent upon the dosage administered. Therapeutic doses of warfarin decrease the plasma amount of the active form of each vitamin K dependent clotting factor made by the liver by approximately 30% to 50%.

An anticoagulant effect generally occurs within 24 hours after drug administration. However, peak anticoagulant effect may be delayed 72 to 96 hours. The duration of action of a single dose of warfarin sodium is 7 to 9 days. The effects of warfarin sodium may become more pronounced as effects of drug resistance decrease over time. Anticoagulants have no direct effect on an established thrombus, nor do they reverse existing tissue damage. However, since a thrombus has occurred the goal of anticoagulant treatment is to prevent further extension of the thrombus and to prevent secondary thrombotic complications which may result in tissue and possibly vital organ damage.

Pharmacokinetics: Warfarin sodium is a racemic mixture of the R- and S-enantiomers. The S-enantiomer exhibits 2-5 times more anticoagulant activity than the R-enantiomer in humans, but generally has a more rapid clearance.

Absorption: Warfarin sodium is essentially completely absorbed after oral administration with peak concentrations generally attained within one hour. Distribution: There are no differences in the apparent volumes of distribution after intravenous and oral administration of single doses of warfarin sodium. Warfarin distributes into a relatively small apparent volume of distribution of about 0.14 liter/kg. A distribution phase lasting 6 to 17 hours is distinguishable after rapid intravenous or oral administration of an aqueous solution. Using a one-compartment model, and assuming complete bioavailability, estimates of the volumes of distribution of R- and S-warfarin are similar to each other and to that of the racemate. Concentrations in fetal plasma approach the maternal values, but warfarin has not been found in human milk. (See WARNINGS - Lactation). Approximately 99% of the drug is bound to plasma proteins.

Metabolism: The elimination of warfarin is almost entirely by metabolism. Warfarin sodium is stereoselectively metabolized by hepatic microsomal enzymes (cytochrome P-450) to inactive hydroxylated metabolites (phenol metabolites) and by reductions to reduced metabolites (warfarin alcohols). The warfarin alcohols have minimal anticoagulant activity. The metabolites are principally excreted into the urine, and to a lesser extent into the bile. The metabolites of warfarin that have been identified include acetyldeswarfarin, two diastereomeric alcohols, 4'-, 6'-, 7'-, 8'- and 10-hydroxywarfarin. The cytochrome P-450 isozymes involved in the metabolism of warfarin include CYP2C9, CYP2C19, CYP2C18, 1A2, and 3A4. CYP2C9 is likely to be the principal form of human liver P-450 which mediates the in vivo anticoagulant activity of warfarin.

Excretion: The terminal half-life of warfarin after a single dose is approximately one week; however, the effective half-life ranges from 23 to 80 hours, with a mean of about 40 hours. The clearance of R-warfarin is generally half that of S-warfarin, thus the volume of excretion is smaller, the half-life of R-warfarin is longer than that of S-warfarin. The half-life of R-warfarin ranges from 37 to 80 hours, while that of S-warfarin ranges from 21 to 43 hours. Studies with concentrated drug have demonstrated that up to 95% of the drug administered dose is recovered in urine. Very little warfarin is excreted unchanged in urine; urinary excretion is in the form of metabolites.

Steadily: There are no significant age-related differences in the pharmacokinetics of racemic warfarin. Clinical pharmacokinetic studies that there is no effect.

Pharmacokinetics: Warfarin is a racemic mixture of two enantiomers, R-warfarin and S-warfarin. S-warfarin is the more active enantiomer. The half-life of S-warfarin is approximately 37-49 hours, while the half-life of R-warfarin is approximately 35-49 hours. The elimination half-life of warfarin is approximately 36-50 hours. The clearance of warfarin is approximately 0.1-0.2 L/kg/day. The volume of distribution is approximately 0.1-0.2 L/kg. Warfarin is metabolized by the liver, primarily by the CYP2C9 and CYP2C19 enzymes. The major metabolites are 7-hydroxywarfarin and 4-hydroxywarfarin. Warfarin is excreted in the urine as glucuronide conjugates. The elimination half-life of warfarin is prolonged in patients with liver disease and in patients taking drugs that inhibit the CYP2C9 and CYP2C19 enzymes.

Pharmacodynamics: Warfarin is an oral anticoagulant that acts by inhibiting the synthesis of vitamin K-dependent clotting factors II, VII, IX, and X. The effect of warfarin is measured by the international normalized ratio (INR). The therapeutic range for INR is typically 2.0-3.0 for most patients. The risk of bleeding increases with INR values above 3.0. Warfarin is used to prevent and treat thromboembolic disorders, such as deep vein thrombosis, pulmonary embolism, and stroke. Warfarin is also used to prevent blood clots in patients with mechanical heart valves. Warfarin is contraindicated in patients with active bleeding, severe liver disease, and severe renal impairment.

Table 1: Summary of Warfarin Pharmacokinetics and Pharmacodynamics

Parameter	Value
Half-life (S-warfarin)	37-49 hours
Half-life (R-warfarin)	35-49 hours
Clearance	0.1-0.2 L/kg/day
Volume of distribution	0.1-0.2 L/kg
Metabolism	CYP2C9, CYP2C19
Major metabolites	7-hydroxywarfarin, 4-hydroxywarfarin
Excretion	Glucuronide conjugates
Therapeutic range (INR)	2.0-3.0
Risk of bleeding	Increases with INR > 3.0

Warfarin Interactions: Warfarin has numerous drug interactions. Drugs that inhibit the CYP2C9 and CYP2C19 enzymes, such as amiodarone, fluconazole, and trimethoprim-sulfamethoxazole, can increase the plasma concentration of warfarin and increase the risk of bleeding. Drugs that induce the CYP2C9 and CYP2C19 enzymes, such as rifampin and carbamazepine, can decrease the plasma concentration of warfarin and decrease the risk of bleeding. Warfarin also interacts with many other drugs, including aspirin, NSAIDs, and other anticoagulants. Patients taking warfarin should be monitored closely for signs of bleeding and should avoid alcohol and high-dose vitamin K.

Table 2: Summary of Warfarin Clinical Trials

Study	Population	Intervention	Control	Primary Outcome
Warfarin vs. Aspirin	Patients with atrial fibrillation	Warfarin	Aspirin	Stroke and systemic embolism
Warfarin vs. Aspirin	Patients with acute coronary syndrome	Warfarin	Aspirin	Stroke and systemic embolism
Warfarin vs. Aspirin	Patients with deep vein thrombosis	Warfarin	Aspirin	Stroke and systemic embolism
Warfarin vs. Aspirin	Patients with pulmonary embolism	Warfarin	Aspirin	Stroke and systemic embolism

Warfarin and Mechanical Heart Valves: Warfarin is used to prevent blood clots in patients with mechanical heart valves. The risk of thromboembolism is high in these patients, and warfarin is the only oral anticoagulant that has been shown to be effective in preventing blood clots. The therapeutic range for INR is typically 2.5-3.5 for patients with mechanical heart valves. Patients taking warfarin for mechanical heart valves should be monitored closely for signs of bleeding and should avoid alcohol and high-dose vitamin K. Warfarin is also used to prevent blood clots in patients with atrial fibrillation, acute coronary syndrome, deep vein thrombosis, and pulmonary embolism.

[illegible]

Western saddlebills are indicated for
large and/or treatment of venders through
and preliminary inspection

Warfarin sodium tablets are indicated for anticoagulation and/or treatment of the thrombotic disorders associated with aortic fibrillation valve replacement.

Warfarin sodium tablets are indicated for the treatment and prevention of thromboembolic events such as stroke and pulmonary embolism after myocardial infarction.

Anticoagulation is contraindicated in a general physical condition or personal in which the hazard of hemorrhage may outweigh the potential clinical benefits of a

Pregnancy: Warfarin sodium is contraindicated in pregnant women who are or may become pregnant because the drug passes through the placenta.

Furthermore, there have been reports of deaths in children born to mothers treated with vertebro during pregnancy.

Everyday characteristics, with or without shaped epiphyses (chondriza) has been reported in pregnant women during the first trimester. Certain abnormalities also have been

ing dorsal midline cystic degeneration of the corpus callosum. Demonstration of midline cerebellar atrophy, and midline cerebellar atrophy, characterized by optic atrophy.

then, blindness, and other central abnormalities have been reported in second and third trimester exposure to organic mercury. In a

kidney, asplenia, omencephaly, spina nerve palsy, hydrocephalus, congenital heart disease, polydactyly, diaphragmatic hernia, corneal

Spontaneous abortion and still birth occur and a higher risk of fetal wastage with the use of warfarin. Low

Women of childbearing potential for anticonceptant therapy should assess the indications critically. If the patient becomes pregnant

this drug, she should be aware of risks to the fetus, and the possibility of the pregnancy should be discussed with her.

Recent or contemplated surgery:
nervous system; (2) eye; (3) trauma
in large open surfaces.

- (1) primary of respiratory tract;
- (2) aneurysms; and
- (3) perforation and perforated ulcers.

Twenty-four identical, schematic of inadequate laboratory facilities. Overheated patients with over- or other lack of air.

Special procedures and other deep procedures with potential for use:

The most serious risks associated with the use of this product are:

The risk of hemorrhage is related to the duration of anticoagulation therapy with sodium warfarin. It is noted in organ and, less frequently, adrenal gangrene of the adrenal gland.

ity and the degree of damage to the lungs and adrenals have in fact in itself in death or permanent appears to be associated with usually appears within a few d

concurrent therapy, in which the
manipulation through debridement
affected tissue, heat, breast or
careful diagnosis is required.
Increase is caused by an under

therapy should be discontinued if the patient is suspected to be the cause of the reaction. If the patient is suspected to be the cause of the reaction, the patient should be treated with appropriate therapy. Although various other causes of the reaction have been reported, the patient should be treated with appropriate therapy.

ered uniformly effective. So on prepressing conditions associated with suboptimal spread the risk of threat

of each parent is a tight Western custom. A narrow door may be affected by the

and dietary vitamin E. Data by periodic determinations of serum cholesterol and International Normalized Ratio (INR) suggest that the

clothing and bathing, and
for control of therapy. Most
PT. When reports and ob-
served concurrently, re-
frain before the therapy

Caution should be observed when using any of the above information in any way. The information is not intended to be used for any purpose other than that for which it was prepared. The information is not intended to be used for any purpose other than that for which it was prepared.

Amiloride—enhances the release of insulin thereby increasing the systemic cholesterol levels.

Systemic allergic reactions can present with a variety of symptoms including hives, wheezing, and anaphylaxis.

itch, gangrene, shrivel /
toot, or toes, foot ailments
abdominal pain, flank or
inefficiency, hypertension

cardiac infarction, pneumonia, polyarteritis, or any other cause due to embolic occlusion of involved visceral organs, the pancreas, spleen,

progressed to necrosis. Purple line syndrome is a nonfatal dermatitis which involved outer of the web 3-10 weeks, or later.

with vertebrae or rotation of this syndrome includes vertebrae and sides of the spine pressure and lateral side and movement.

of the color over time. It is reported to be reversible and occurs in the absence of any significant change in the affected area.

A severe outbreak (50 thrombocytopenic) was detected since has been increased risk of post-transfusion thrombocytopenia. The decision to stop

The outcome is seen following conditions judgment in which they are weighed against the following:

During mother's in care by certain national is preferable to infants have not been

5

PERCAUTIONS
Periodic determination of PT/INR or other suitable
coagulation test is essential!

drugs may interact with warfarin sodium through pharmacokinetic or pharmacodynamic mechanisms. Pharmacokinetic mechanisms for drug interactions with warfarin sodium are: an synergism (impaired hemostasis, reduced clotting factor synthesis), competitive antagonism (vitamin K), and altered physiological control loop for vitamin K metabolism (hepatotoxic resistance). Pharmacodynamic mechanisms for drug interactions with warfarin sodium are: enhanced enzyme induction, enzyme inhibition, and reduced protein binding. It is important to note that some drugs may interact by more than one mechanism.

The following table, alone or in combination, may be supplements for **ENCORBET 50/100**.

leaky gut disorders:
 infectious tapeworms
 ischemic
 hyperlipidemia
 post-neutroci state
 disaccharose
 vitamin K deficiency

Potential drug interactions with vericor sodium
are listed below by drug class and by specific drug.

Changes of Type

- [illegible]

[illegible]

7

patients with potential to exhibit greater than

Obtained by (state dosage adjustment) if renal impairment is indicated. Response may be preferable for other therapy.

If minor bleeding progresses to major bleeding (see 5 to 7.5 mg (range up to 50 mg) warfarin sodium).

5. In emergency situations of severe hemorrhage, clotting factors (200 to 500 ml of plasma whole blood or fresh frozen plasma or by giving commercial Factor IX Concentrate).

A risk of bleeding and other viral diseases is associated with the use of these blood products. Factor IX concentrates are associated with an increased risk of thrombosis. Therefore, these preparations should be used only in exceptional or life-threatening bleeding episodes secondary to warfarin sodium overdosage.

Purified Factor IX preparations should not be used because they cannot increase the level of prothrombin factor VII and factor X which are also depressed along with the level of Factor IX as a result of warfarin sodium treatment. Packed red blood cells may also be given if significant blood loss has occurred. Infusions of blood or plasma should be administered carefully to avoid precipitating pulmonary edema in elderly patients or patients with heart disease.

DOSEAGE AND ADMINISTRATION

The dosage and administration of warfarin sodium must be individualized for each patient according to the patient's PT/INR response to the drug. The dosage should be adjusted based upon the patient's PT/INR (See Laboratory Control below for full discussion on INR).

Thrombotic Thrombocytopenia (including pulmonary embolism): Acceptable clinical evidence indicates that an INR of 2.0-3.0 is sufficient for prophylaxis and treatment of venous thromboembolism and mesenteric and renal thromboses with higher INRs. **Renal Dysfunction:** Few recent clinical trials evaluated the effects of warfarin in patients with renal dysfunction. (A) Data suggest that the effects of warfarin on bleeding thrombotic events including venous thromboses were similar at either moderately high INR (2.0-4.5) or low INR (1.4-3.0). There was a significant reduction in major bleeding at the low INR. Limited data from clinical studies in patients with renal dysfunction are not available. The results of non-randomized clinical studies (see the American College of Chest Physicians (ACCP) and the American College of Physicians (ACP) recommendations for the use of warfarin 2.0-3.0 in patients with renal dysfunction).

Post-operative patients: In post-operative patients, warfarin sodium therapy should be initiated 1-2 weeks after surgery and dosage should be adjusted to maintain an INR of 2.0-3.0 long-term. The recommendation is based on the results of the WARIS study in which treatment was initiated 2 to 4 weeks after the operation in patients thought to be at an increased risk of bleeding complications or on surgery therapy. Maintenance of warfarin sodium therapy at the lower end of the INR range is recommended. **Mechanical and Bioprosthetic Heart Valves:** In patients with mechanical heart valves, long-term prophylaxis with warfarin to an INR of 2.5-3.5 is recommended. In patients with bioprosthetic heart valves, based on limited data, the American College of Chest Physicians recommends warfarin therapy to an INR of 2.0-3.0 for 12 weeks after valve insertion. In patients with additional risk factors such as atrial fibrillation or prior thromboembolism, continuation should be given for longer term therapy. **Recurrent Systemic Embolism:** In cases where the risk of thromboembolism is great, such as in patients with recurrent systemic embolism, a higher INR may be required.

An INR of greater than 4.0 appears to provide no additional therapeutic benefit to most patients and is associated with a higher risk of bleeding.

Initial Dosage: The dosage of warfarin sodium must be individualized according to patient's sensitivity to the drug as indicated by the PT/INR. Use of a large loading dose may increase the incidence of hemorrhage and other complications, does not offer more rapid protective against thrombotic formation, and is not recommended. Low initiation doses are recommended for elderly and/or debilitated patients and patients with potential to achieve greater than expected PT/INR response to warfarin sodium (see PRECAUTIONS). It is recommended that warfarin sodium therapy be initiated with a dose of 2 to 5 mg per day with dosage adjustments based on the results of PT/INR determinations.

Maintenance: Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be guided by the patient's prothrombin response.

Duration of Therapy: The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Missed Dose: The anticoagulant effect of warfarin sodium persists beyond 24 hours. If the patient forgets to take the prescribed dose of warfarin sodium at the scheduled time, the dose should be taken as soon as possible on the same day. The patient should not take the missed dose by doubling the daily dose to make up for missed doses, but should refer back to his or her physician.

Intravenous Route of Administration: Warfarin sodium for injection provided in intravenous administration route for patients who cannot receive oral drugs. The I.V. dosages would be the same as those that would be given orally if the patient could take the drug by the oral route. Warfarin sodium for injection should be administered as a slow bolus injection over 1 to 2 minutes into a peripheral vein. It is not recommended for intramuscular administration. The vial should be resuspended with 2.7 mL of sterile water for injection and resuspended for particulate matter and discoloration immediately prior to use. Do not use if either particulate matter and/or discoloration is noted after resuspension. Warfarin sodium for injection is chemically and physically stable for 4 hours at room temperature. It does not contain any antimicrobial preservative and, thus, care must be taken to ensure the sterility of the prepared solution. The vial is not recommended for multiple use and unused solution should be discarded.

LABORATORY CONTROL: The PT reflects the depression of vitamin K dependent factors VII, X and II. There are several modifications of the one-stage PT and the physician should become familiar with the specific method used in his laboratory. The degree of anticoagulation indicated by any range of PTs may be altered by the type of thromboplastin used, the appropriate therapeutic range must be based on the experience of each laboratory. The PT should be determined daily after the administration of the initial dose until PT/INR results stabilize in the therapeutic range. Interval between subsequent PT/INR determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin sodium in order to maintain the individual within the therapeutic range. Acceptable intervals for PT/INR determinations are normally within the range of one to four weeks after a stable dosage has been determined. To ensure adequate control, it is recommended that subsequent PT tests are done using either warfarin products are interchanged with warfarin sodium and that if other medications are administered with warfarin sodium (see PRECAUTIONS).

Different thromboplastin reagents vary markedly in their sensitivity to sodium warfarin-induced effects on PT. To obtain the appropriate diagnostic response it is essential to be familiar with the sensitivity of the thromboplastin reagent used in the laboratory and to communicate to the International Reference Preparation (IRP), a common thromboplastin reagent prepared from human brain.

A review of understanding the PT is an anticoagulant control was introduced by the World Health Organization in 1962. It is based upon the determination of an international reference plasma (IRP) which provides a common basis for comparison of PT results and interpretation of therapeutic ranges. The INR system of reporting is based on a separate relationship between the PT ratios of the test and reference preparations. The INR is the PT ratio that would be obtained if the International Reference Preparation (IRP) which has an ISI of 1.0, were used to perform the test. Early clinical studies of oral anticoagulants, which formed the basis for recommended therapeutic ranges of 1.5 to 2.5 based on a common PT, used sensitive human brain thromboplastin. When using the less sensitive rabbit brain thromboplastins commonly employed in PT today, adjustments must be made to the targeted PT range that reflect this decrease in sensitivity. The INR can be calculated as: $INR = \frac{\text{observed PT ratio}}{\text{ISI}}$

where the ISI (International Sensitivity Index) is the correction factor in the equation that relates the PT ratio of the local reagent to the reference preparation and is a measure of the sensitivity of a given thromboplastin to reduction of vitamin K-dependent coagulation factors; the lower the ISI, the more "sensitive" the reagent and the closer the derived INR will be to the observed PT ratio.

The proceedings and recommendations of the 1992 National Conference on Antithrombotic Therapy¹⁻⁴ review and evaluate data related to oral anticoagulant therapy and the sensitivity of thromboplastin reagents and provide additional guidelines for achieving the appropriate therapeutic regimen.

The coverage of the INR to PT ratios for the therapeutic range (INR 2.0-3.0) and more intense (INR 2.5-3.5) therapeutic range recommended by the ACCP for thrombotic events over a range of ISI ratios is shown in Table 3.1.

INR	ISI	PT Ratio
2.0	1.0	2.0
2.5	1.0	2.5
3.0	1.0	3.0
3.5	1.0	3.5
4.0	1.0	4.0
4.5	1.0	4.5
5.0	1.0	5.0
5.5	1.0	5.5
6.0	1.0	6.0
6.5	1.0	6.5
7.0	1.0	7.0
7.5	1.0	7.5
8.0	1.0	8.0
8.5	1.0	8.5
9.0	1.0	9.0
9.5	1.0	9.5
10.0	1.0	10.0
10.5	1.0	10.5
11.0	1.0	11.0
11.5	1.0	11.5
12.0	1.0	12.0
12.5	1.0	12.5
13.0	1.0	13.0
13.5	1.0	13.5
14.0	1.0	14.0
14.5	1.0	14.5
15.0	1.0	15.0
15.5	1.0	15.5
16.0	1.0	16.0
16.5	1.0	16.5
17.0	1.0	17.0
17.5	1.0	17.5
18.0	1.0	18.0
18.5	1.0	18.5
19.0	1.0	19.0
19.5	1.0	19.5
20.0	1.0	20.0
20.5	1.0	20.5
21.0	1.0	21.0
21.5	1.0	21.5
22.0	1.0	22.0
22.5	1.0	22.5
23.0	1.0	23.0
23.5	1.0	23.5
24.0	1.0	24.0
24.5	1.0	24.5
25.0	1.0	25.0
25.5	1.0	25.5
26.0	1.0	26.0
26.5	1.0	26.5
27.0	1.0	27.0
27.5	1.0	27.5
28.0	1.0	28.0
28.5	1.0	28.5
29.0	1.0	29.0
29.5	1.0	29.5
30.0	1.0	30.0
30.5	1.0	30.5
31.0	1.0	31.0
31.5	1.0	31.5
32.0	1.0	32.0
32.5	1.0	32.5
33.0	1.0	33.0
33.5	1.0	33.5
34.0	1.0	34.0
34.5	1.0	34.5
35.0	1.0	35.0
35.5	1.0	35.5
36.0	1.0	36.0
36.5	1.0	36.5
37.0	1.0	37.0
37.5	1.0	37.5
38.0	1.0	38.0
38.5	1.0	38.5
39.0	1.0	39.0
39.5	1.0	39.5
40.0	1.0	40.0
40.5	1.0	40.5
41.0	1.0	41.0
41.5	1.0	41.5
42.0	1.0	42.0
42.5	1.0	42.5
43.0	1.0	43.0
43.5	1.0	43.5
44.0	1.0	44.0
44.5	1.0	44.5
45.0	1.0	45.0
45.5	1.0	45.5
46.0	1.0	46.0
46.5	1.0	46.5
47.0	1.0	47.0
47.5	1.0	47.5
48.0	1.0	48.0
48.5	1.0	48.5
49.0	1.0	49.0
49.5	1.0	49.5
50.0	1.0	50.0
50.5	1.0	50.5
51.0	1.0	51.0
51.5	1.0	51.5
52.0	1.0	52.0
52.5	1.0	52.5
53.0	1.0	53.0
53.5	1.0	53.5
54.0	1.0	54.0
54.5	1.0	54.5
55.0	1.0	55.0
55.5	1.0	55.5
56.0	1.0	56.0
56.5	1.0	56.5
57.0	1.0	57.0
57.5	1.0	57.5
58.0	1.0	58.0
58.5	1.0	58.5
59.0	1.0	59.0
59.5	1.0	59.5
60.0	1.0	60.0
60.5	1.0	60.5
61.0	1.0	61.0
61.5	1.0	61.5
62.0	1.0	62.0
62.5	1.0	62.5
63.0	1.0	63.0
63.5	1.0	63.5
64.0	1.0	64.0
64.5	1.0	64.5
65.0	1.0	65.0
65.5	1.0	65.5
66.0	1.0	66.0
66.5	1.0	66.5
67.0	1.0	67.0
67.5	1.0	67.5
68.0	1.0	68.0
68.5	1.0	68.5
69.0	1.0	69.0
69.5	1.0	69.5
70.0	1.0	70.0
70.5	1.0	70.5
71.0	1.0	71.0
71.5	1.0	71.5
72.0	1.0	72.0
72.5	1.0	72.5
73.0	1.0	73.0
73.5	1.0	73.5
74.0	1.0	74.0
74.5	1.0	74.5
75.0	1.0	75.0
75.5	1.0	75.5
76.0	1.0	76.0
76.5	1.0	76.5
77.0	1.0	77.0
77.5	1.0	77.5
78.0	1.0	78.0
78.5	1.0	78.5
79.0	1.0	79.0
79.5	1.0	79.5
80.0	1.0	80.0
80.5	1.0	80.5
81.0	1.0	81.0
81.5	1.0	81.5
82.0	1.0	82.0
82.5	1.0	82.5
83.0	1.0	83.0
83.5	1.0	83.5
84.0	1.0	84.0
84.5	1.0	84.5
85.0	1.0	85.0
85.5	1.0	85.5
86.0	1.0	86.0
86.5	1.0	86.5
87.0	1.0	87.0
87.5	1.0	87.5
88.0	1.0	88.0
88.5	1.0	88.5
89.0	1.0	89.0
89.5	1.0	89.5
90.0	1.0	90.0
90.5	1.0	90.5
91.0	1.0	91.0
91.5	1.0	91.5
92.0	1.0	92.0
92.5	1.0	92.5
93.0	1.0	93.0
93.5	1.0	93.5
94.0	1.0	94.0
94.5	1.0	94.5
95.0	1.0	95.0
95.5	1.0	95.5
96.0	1.0	96.0
96.5	1.0	96.5
97.0	1.0	97.0
97.5	1.0	97.5
98.0	1.0	98.0
98.5	1.0	98.5
99.0	1.0	99.0
99.5	1.0	99.5
100.0	1.0	100.0

10

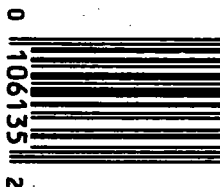
NDC 52180-211-24 in bottles of 100 Tablets
 NDC 52180-211-25 in bottles of 1000 Tablets
 Warfarin Sodium Tablets USP, 4 mg are white, uncoated, compressed tablets, engraved with "W" above and "112" below the imprint on one side and 4 on the other side are supplied as follows:
 NDC 52180-212-24 in bottles of 100 Tablets
 NDC 52180-212-25 in bottles of 1000 Tablets
 Warfarin Sodium Tablets USP, 5 mg are white, uncoated, compressed tablets, engraved with "W" above and "112" below the imprint on one side and 5 on the other side are supplied as follows:
 NDC 52180-213-24 in bottles of 100 Tablets
 NDC 52180-213-25 in bottles of 1000 Tablets
 Warfarin Sodium Tablets USP, 7.5 mg are white, uncoated, compressed tablets, engraved with "W" above and "114" below the imprint on one side and 7.5 on the other side are supplied as follows:
 NDC 52180-214-24 in bottles of 100 Tablets
 NDC 52180-214-25 in bottles of 1000 Tablets
 Warfarin Sodium Tablets USP, 10 mg are white, uncoated, compressed tablets, engraved with "W" above and "115" below the imprint on one side and 10 on the other side are supplied as follows:
 NDC 52180-215-24 in bottles of 100 Tablets
 NDC 52180-215-25 in bottles of 1000 Tablets
 Product may light flares at controlled room temperature 15°-30°C (59°-86°F). Store in a light, light-resistant container as directed in the U.S.P.
 Caution: Federal law prohibits dispensing without prescription.

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Manufactured by:
 INVAMED, INC.
 Dayton, NJ 08510 USA

Date of Revision: December 1988
 L-1001; MF P006A



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040196

CHEMISTRY REVIEW(S)

1. ADDENDUM TO CHEMISTRY REVIEW NO. 3
2. ANDA # 40-196
3. NAME AND ADDRESS OF APPLICANT
Invamed Inc.
Attention: Mahendra Patel, Ph.D.
2400 Route 130 North
Dayton, NJ 08810
4. BASIS OF SUBMISSION
The applicant certifies that to the best of their knowledge that all patents and exclusivities with respect to the subject drug product have expired.
5. SUPPLEMENT(s)
N/A
6. PROPRIETARY NAME
7. NONPROPRIETARY NAME
Warfarin Sodium Crystalline Clathrate
8. SUPPLEMENT PROVIDE FOR:
N/A
9. AMENDMENTS AND OTHER DATES:
June 14, 1996-- Original Submission
August 8, 1996-- Acknowledgment receipt
November 15, 1996- Deficiency letter
December 20, 1996-- Amendment
April 3, 1997-- Labeling review
June 9, 1997-- Deficiency letter
June 27, 1997-- Amendment
July 8, 1997-- Telecom
July 8, 1997-- Telecom Amendment
September 25, 1997- Telecom--E. Ramos
September 25, 1997- Telecom amendment
September 25, 1997- Telecom--B. Arnwine
September 25, 1997- Telecom amendment
10. PHARMACOLOGICAL CATEGORY
Anticoagulant
11. Rx or OTC
Rx
12. RELATED Drug Master Files

13. DOSAGE FORM 14. POTENCY
Tablets 1, 2, 2.5, 4, 5, 7.5 & 10 mg

15. CHEMICAL NAME AND STRUCTURE
Warfarin Sodium USP
 $C_{19}H_{15}NaO_4$; M.W. = 330.32

3-(α -Acetonylbenzyl)-4-hydroxycoumarin sodium salt.
CAS [129-06-6]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
A commitment to provide copies of the executed batch records for the 2 mg and 10 mg dosage forms including finished product release data (COAs), and to place these batches in accelerated stability studies is appended. The firm agreed to provide the batch records and pertinent data as soon as it becomes available and to submit it as a 'special Correspondence Post-Approval.' These data should be found acceptable by OGD prior to marketing the final drug products. The stability data is not a requirement prior to marketing the product, however, it should be submitted as soon as it becomes available.

The stability specifications forms, for each dosage form, were revised to reflect the deletion of the IPA analysis since this was considered to be unnecessary.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval letter to issue.

19. REVIEWER: DATE COMPLETED:
Edwin Ramqs September 26, 1997

9/26/97
126/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040196

BIOEQUIVALENCE REVIEW(S)

ANDA 40-196

Invamed Inc.
Attention: Mahendra Patel, Ph.D.
2400 Route 130 North
Dayton NJ 08810
|||||

25 198

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Warfarin Sodium Tablets USP, 1 mg, 2 mg, 2.5 mg, 4 mg, 5 mg, 7.5 mg, 10 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.
2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

NOV 18 1996

Warfarin Sodium Tablets
1, 2, 2.5, 4, 5, 7.5 & 10 mg
ANDA #40-196
Reviewer: A.P.Patel
File: xlapatel\40196sdw.696

Invamed, Inc.
Dayton, NJ
Submission Date:
June 14, 1996

Review of Two BE Studies, Dissolution Data and Waiver Requests

Objectives:

Review of Invamed's two *in vivo* bioequivalence studies comparing its 2 mg and 10 mg Warfarin Sodium Tablets to DuPont-Merck's 2 mg and 10 mg, Coumadin® Tablets under fasting conditions. The firm submitted *in vitro* dissolution data for review and waiver from bioequivalence requirements for their 1, 2.5, 4, 5, and 7.5 mg warfarin sodium tablets.

Introduction:

Warfarin Sodium is an anticoagulant drug. The drug acts by inhibiting the synthesis of vitamin K dependent coagulation factors. It is indicated for venous thrombosis, pulmonary embolism, systemic embolism and thromboembolic complications associated with myocardial infarction, cardiac valve replacement, atrial fibrillation and stroke. The oral absorption of Coumadin is complete. Maximum plasma concentration occurs in 1 to 9 hours. It is approximately 97% bound to plasma albumin. An anticoagulation effect generally occurs within 24 hours. However, peak anticoagulant effect may be delayed 72 to 96 hours and its duration of action may persist for 4 to 5 days. The half-life of warfarin sodium is about 2.5 days. The warfarin is metabolized in the liver to inactive metabolites. Coumadin is commonly used at a dose of 2 to 10 mg/day.

Warfarin is marketed as Coumadin® Tablets and Injection (DuPont-Merck).

Summary of Bioequivalence Study Procedures:

A. BE Study under Fasting Conditions:

2 mg bio-study

1. Protocol and Study# P95-242

2. Objective of the study:

The objective of this study is to determine the bioequivalence of two warfarin sodium formulations after administration of single doses to healthy volunteers under fasting conditions.

3. Study Design:

A randomized, single-dose, two-period, two-treatment, two-sequence crossover study (four week wash-out period) was conducted assessing the relative bioavailability of Invamed's Warfarin Sodium 2x2 mg tablets vs. DuPont-Merck's Coumadin® 2x2 mg tablets under fasting condition.

4. Study sites:

Clinical Facility:

Analytical Facility:

5. **Study dates:** Period 1 October 15 - 25, 1995
Period 2 November 12 - 22, 1995
6. **Drug Products:**
2 mg Tablets:
A. Test: 2 mg Warfarin Sodium Tablets (Invamed, Lot #D950809, batch size
B. Reference: 2 mg Coumadin® Tablets (DuPont-Merck, Lot #EHJ245A, Exp. 8/97).
All doses were administered with 240 mL water following an overnight fast.
7. **Subjects:** Twenty-six healthy male volunteer subjects were recruited for this study with a mean age of 22.8 ± 5.3 years, and within 10% of their ideal weight as specified in the protocol. All subjects were selected based on the medical history, physical examination and clinical laboratory evaluations showing absence of any clinically significant findings. Inclusion and exclusion criteria in the protocol were followed in the selection of the subjects.
8. **Confinement:** At least 8 hours pre-dose to at least 24 hours post-dose administration, each period. The subjects were housed and fed at the clinical facility.
9. **Food and fluid intake:** Standardized meals and beverages. No caffeine or xanthine-containing food or drink was allowed during confinement. The drug products were administered with 240 mL of water following 8 hour fast. Water was allowed ad lib. after 2 hours post-dose.
10. **Washout period:** 4 weeks
11. **Blood samples:** In each period, 10 mL of blood samples were collected in EDTA containing purple-top tubes at 0, 0.17, 0.33, 0.50, 0.75, 1, 1.50, 2, 3, 4, 6, 8, 10, 14, 24, 48, 72, 96, 144, 192, and 240 hours. Plasma was separated and all plasma samples were stored frozen at -20°C or below until analyzed.
12. **Subject safety monitoring:** Subjects were asked to spontaneously report any signs or symptoms that might be related to the drug products.
13. **Adverse events:** Following each dosing period subjects were asked to report any signs or symptoms judged to be drug related.
14. **Analytical procedure:**
15. **Pharmacokinetics and statistical analysis:** Statistical analyses were performed on the pharmacokinetics parameters for warfarin. The 90% confidence intervals were calculated for AUC_t, AUC_i and C_{max}.
- B. **BE Study for 10 mg Warfarin Sodium Tablets:**
 1. Protocol and Study # P95-243

2. **Objective of the study:**

The objective of this study is to determine the bioequivalence of two warfarin sodium formulations after administration of single doses to healthy volunteers under fasting conditions.

3. **Study design:** Randomized, single-dose, two-way crossover study under fasting conditions.

4. **Study sites:** As described under 2 mg Warfarin Sodium Tablet

Institutional Review Board Approval: Protocol approved by IRB

5. **Study dates:** Period 1 October 1- 11, 1995
Period 2 October 29 - November 8, 1995

6. **Drug Products:**

A. Test: 10 mg Warfarin Sodium Tablets (Invamed, Lot #D950808, batch size

B. Reference: 10 mg Coumadin® Tablets (DuPont-Merck, Lot #EHB042A, Exp. 1/97).

All doses were administered with 240 mL of water following an overnight fast.

7. **Subjects:** Twenty-six subjects who entered the clinical study were normal healthy male volunteers with a mean age of 22.8 ± 3.7 years, and within 10% of their ideal weight as specified in the protocol. All subjects were selected based on the medical history, physical examination and clinical laboratory evaluations showing absence of any clinically significant findings. Inclusion and exclusion criteria in the protocol were followed in the selection of the subjects.

8. **Confinement, Food and fluid intake, Blood samples, Subject safety monitoring, adverse events, Analytical procedure, Pharmacokinetics and statistical analysis** is same as that described under the 2 mg Warfarin Sodium-fasting study.

III. **Validation of Assay Method for Plasma Samples:**

IV. *In Vivo* BE Study Results with Statistical Analysis:

A. Study under fasting conditions:

2 mg Warfarin Sodium Tablets:

A total of 26 subjects participated in the study and 25 subjects completed two periods of clinical study successfully. Subject #11 dropped out for reasons not related to the study and data not included in the analysis. There were three missing samples, subject #12 period 1, hours 72, 96, and 144. A total of 5 samples were repeated for analysis.

Adverse events: were followed according to the protocol of the study. Thirty-six adverse events were reported in thirteen of twenty-six subjects dosed. Nature of events included bronchitis, conjunctivitis, cough, earache, eye abnormality, fatigue, headache, hypertonia, laceration, malaise, pain, pharyngitis, rhinitis and tonsillitis. There were no serious adverse events.

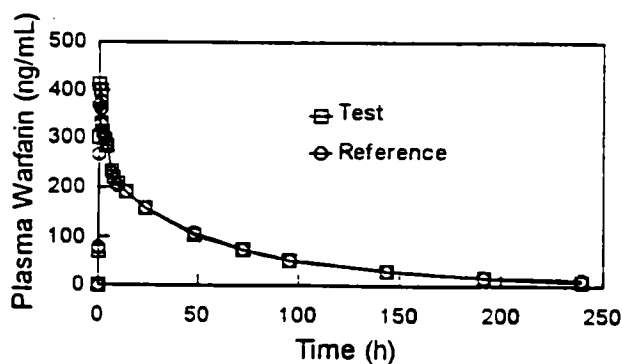
1. Mean plasma levels

The mean plasma levels for the test and reference products are comparable as shown in Table 9. The test/reference ratios for the mean plasma levels range from 0.87 to 1.13.

Table 9. Mean plasma warfarin levels (ng/mL) for test and reference products (n=25).

Time (h)	Test (ng/mL)	Reference (ng/mL)	Ratio (T/R)
0	0	0	
0.17	69.06	76.48	0.90
0.33	302.61	268.32	1.13
0.5	412.44	368.6	1.12
0.75	400.2	377.72	1.06
1	372.68	361.84	1.03
1.5	331.52	331.32	1.00
2	315.68	313.12	1.01
3	295.28	301.12	0.98
4	284.04	290.36	0.98
6	235.72	231.08	1.02
8	220.64	216.12	1.02
10	207.04	203.92	1.02
14	191.88	191.24	1.00
24	158.76	157.64	1.01
48	104.66	105.69	0.99
72	71.32	71.42	1.00
96	53.556	50.41	1.06
144	31.16	31.53	0.99
192	18.532	18.96	0.98
240	11.47	13.22	0.87

Mean Plasma Warfarin Sodium 2 mg bio-study



2. **Summary of Pharmacokinetics Data:** Described in table 10 and 11.

Table 10.

Non-transformed parameters

	Test Mean (CV%)	Reference Mean (CV%)	Ratio (T/R)
AUC _{0-t} (ng*hr/mL)	15780.11 (22)	15934.67 (22)	0.99
AUC _{0-inf} (ng*hr/mL)	17305.15 (22)	17418.26 (22)	0.99
C _{max} (ng/mL)	441.72 (18)	425.28 (19)	1.04
Tmax	0.84 (129)	0.88 (79)	0.95
Kelm	0.011 (21)	0.011 (23)	1.00
Thalf (h)	63.46 (23)	63.99 (19)	0.99

Table 11.

90% C.I. Limits of Ln-transformed parameters:

Parameter	LS Means (CV%) (Test)	LS Means (CV%) (Reference)	T/R	90% Confidence Interval
LNAUC _{0-t}	9.64 (2.5)	9.65 (2.4)	1.00	95.5; 102
LNAUC _{0-inf}	9.73 (2.4)	9.74 (2.4)	1.00	96.1; 102
LNC _{max}	6.08 (3.1)	6.04 (3.2)	1.01	98.2; 111

The 90% C.I. are within the Agency's bioequivalence requirements, between 80% - 125%, fasting study is acceptable. The ratio of test/reference for pharmacokinetics parameters are not different from each other.

B. **Study under fasting Conditions:**
10 mg Warfarin Sodium tablets

The study had 24 subjects completing the clinical study successfully. Subject #21 during period one elected to withdraw from the study, not related to the study medication. Subject #11 failed to report for period II of the study and was dropped from the study. Data from subject #21 and #11 were not included for analysis. Subject #15, periods 1 and 2, hour 144 not drawn at the clinic. A total of 11 samples were repeated for analysis.

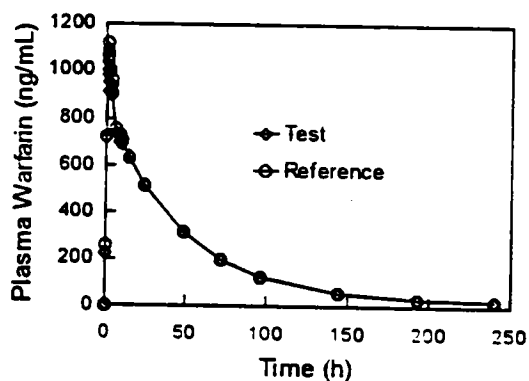
1. Mean plasma levels

Table 12 shows the plasma warfarin-time data for bio-study.

Table 12. Mean Plasma Warfarin for 10 mg bio-study

Time (h)	Test (ng/mL)	Reference (ng/mL)	Ratio (T/R)
0	0	0	
0.17	224.87	263	0.86
0.33	716.96	720.16	1.00
0.5	908.46	1060.13	0.86
0.75	979.14	1115.92	0.88
1	1005.98	1086.04	0.93
1.5	951.69	1045.13	0.91
2	941.29	1001.46	0.94
3	937.5	958.5	0.98
4	891.83	903.38	0.99
6	736.79	752.25	0.98
8	700.58	727.67	0.96
10	691.29	700.92	0.99
14	635.25	633.92	1.00
24	513.25	512.46	1.00
48	318	316.88	1.00
72	199.63	202.73	0.98
96	131.08	129.71	1.01
144	62.63	63.9	0.98
192	36.85	35.79	1.03
240	25	23.77	1.05

Mean Plasma Warfarin (10 mg Study)



2. **Summary of Pharmacokinetics Data:** Described in table 13 and 14.

Table 13. Non-transformed parameters

Parameter	Test Means (CV%)	Reference Means (CV%)	Ratio T/R
AUC _{0-t} (ng*hr/mL)	45168.28 (11.7)	45401.83 (12.1)	0.99
AUC _{0-inf} (ng*hr/mL)	46976.05 (12.5)	47045.30 (12.5)	1.00
C _{max} (ng/mL)	1245 (21.0)	1302.54 (16.1)	0.96
Tmax	1.21 (91.4)	0.98 (75.7)	1.23
Kelm	0.015 (11.9)	0.015 (10)	1.00
Thalf (h)	48.03 (12.7)	47.01 (9.8)	1.02

Table 14. 90% C.I.Limits of Ln-transformed parameters:

Parameter	LS Means (CV%) (Test)	LS Means (CV%) (Reference)	T/R	90% Confidence Interval
LNAUC _{0-t}	10.71 (1.15)	10.72 (1.21)	1.00	95.5; 102
LNAUC _{0-inf}	10.75 (1.2)	10.75 (1.25)	1.00	96.1; 102
LNC _{max}	7.11 (2.9)	7.16 (2.25)	0.99	98.2; 111

The 90% C.I. are within the Agency's bioequivalence requirements, between 80% - 125%, fasting study is acceptable. The ratio of test/reference for pharmacokinetics parameters are not different from each other.

V. **Request for Waiver of Bioequivalence Testing for Warfarin Sodium Tablets, 1 mg, 2.5 mg, 4 mg, 5 mg, and 7.5 mg**

In support of this request, the firm has submitted, two *in vivo* bioequivalence studies, *in vitro* comparative dissolution tests, and comparative formulations for all strengths of the firm's Warfarin Sodium Tablets.

Proportional formulation of test 2 mg and 10 mg tablets and test 1, 2.5, 4, 5, and 7.5 mg tablets is shown in Tables 15 and 16. Comparative dissolution data of test 1, 2.5, 4, 5, and 7.5 mg and reference 1, 2.5, 4, 5, and 7.5 mg tablets are acceptable (Table 18). Waiver from bio-study for test 1, 2.5, 4, 5, and 7.5 mg tablets may be granted.

VI. **Formulation**

Table 15. shows the composition of the test products, 1, 2, 2.5, 4, 5, 7.5 and 10 mg Warfarin Sodium Tablets made by Invamed. All strengths are proportional in active and inactive ingredients to 2 mg and 10 mg bio-study formulations.

Table 15: Quantitative List of Components of Warfarin Sodium Tablets

	1 mg	2 mg	2.5 mg	4 mg	5 mg	7.5 mg	10 mg
Ingredients	mg/Tablet						
Warfarin Sodium Clathrate, USP 23*	1.085	2.17	2.713	4.34	5.425	8.138	10.85
Mannitol, USP**							
Corn Starch							
Lactose Monohydrate, NF							
Hydroxypropyl Methylcellulose							
Purified Water, USP23***							
Magnesium Stearate							
D&C Red #6							
FD&C Blue #2							
FD&C Red #40							
D&C Yellow #10							
FD&C Yellow #6							
FD&C Blue #1							
Total Weight	200	200	200	200	200	200	200

* Weight of warfarin sodium equivalent to strength of the respective tablet

** adjusted for constant tablet weight

*** For manufacturing purposes only

Table 16. Ratio of tablet ingredients with respect to 10 mg Warfarin tablet ingredients

Ingredients	1 mg	2 mg	2.5 mg	4 mg	5 mg	7.5 mg	10 mg
Warfarin Sodium Clathrate 23*	0.1	0.2	0.25	0.4	0.5	0.75	1.0
Mannitol, USP**							
Corn Starch							
Lactose Monohydrate, NF							
Hydroxypropyl Methylcellulose							
Magnesium Stearate							

VII. In Vitro Testing

1. Potency and content uniformity

Assay and content uniformity data are summarized for the test and reference products in Table 17 and are acceptable. The batch size of the test products was tablets.

Table 17. Potency and Content Uniformity

Product	Lot No.	Potency, %	% Content uniformity (%CV)
COUMADIN 10 mg	EHB042A	101.5	100.5 (0.9)
INVAMED 10 mg	D950808	99.7	98.9 (1.3)
COUMADIN 2 mg	EHJ245A	101.0	99.2 (1.1)
INVAMED 2 mg	D950809	100.7	99.5 (0.5)
COUMADIN 7.5 mg	EHK265A	98.1	100.5 (1.0)
INVAMED 7.5 mg	D950801	102.2	99.8 (0.7)
COUMADIN 5 mg	EHN306A	97.9	99.8 (0.7)
INVAMED 5 mg	D950810	101.8	99.8 (0.6)
COUMADIN 4 mg	HC053A	98.0	100.1 (0.7)
INVAMED 4 mg	D950811	102.2	99.6 (0.8)
COUMADIN 2.5 mg	EJA003A	97.4	95.4 (2.0)
INVAMED 2.5 mg	D950806	101.2	98.0 (0.6)
COUMADIN 1 mg	JB057A	98.9	97.9 (3.1)
INVAMED 1 mg	D950901	98.5	100.7 (0.6)

2. Dissolution Testing:

Comparative dissolution tests were conducted by the firm on its Warfarin Sodium tablets, 1 mg, 2 mg, 2.5 mg, 4 mg, 5 mg, 7.5 mg, and 10 mg, and compared to Coumadin[®] tablets, 1 mg, 2 mg, 2.5 mg, 4 mg, 5 mg, 7.5 mg, and 10 mg, respectively. The method and results are presented in Table 18, and are acceptable.

Table 18 In Vitro Dissolution Testing

Table 18 In Vitro Dissolution Testing			
Generic Drug:	Warfarin Sodium		
Dose Strength:	1 mg, 2 mg, 2.5 mg, 4 mg, 5 mg, 7.5 mg and 10 mg		
ANDA #:	40-196		
Firm:	Invamed, Inc.		
I. Conditions for Dissolution Testing:			
USP XXIII Apparatus:	2 (Paddle)	RPM: 50	
No. Units Tested:	12		
Medium:	Deaerated Water	Volume: 900 ml	Temperature: 37°C
Tolerance:	NLT of warfarin (Q) in 30 minutes		
Reference Drug:	Coumadin ^R Tablets (DuPont-Merck); Strengths: see above		
Assay Methodology:			

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product LOT# D950901 Strength (mg): 1			Reference Product LOT # JB057A Strength (mg): 1		
	Mean %	Range	%CV	Mean %	Range	%CV
10	88.8		7.4	76.7		16.1
20	99.5		1.1	101.3		3.2
30	99.3		1.1	100.8		2.6
40	99.5		0.9	101.1		3.1
Sampling Times (Minutes)	Test Product LOT # D950809 Strength (mg): 2			Reference Product LOT # EHJ245A Strength (mg): 2		
	Mean %	Range	%CV	Mean %	Range	%CV
10	78.8		8.6	60.3		28.1
20	97.4		1.3	101.7		2.6
30	98.0		1.1	100.9		2.7
40	99.5		1.4	100.8		2.2
Sampling Times (Minutes)	Test Product LOT # D950806 Strength (mg): 2.5			Reference Product LOT # EJA003A Strength (mg): 2.5		
	Mean %	Range	%CV	Mean %	Range	%CV
10	78.0		7.4	53.1		18.0
20	97.3		1.4	98.0		1.5
30	96.5		0.6	98.2		2.0
40	97.2		0.5	99.4		2.3
Sampling Times (Minutes)	Test Product LOT # D950811 Strength (mg): 4			Reference Product LOT # HC053A Strength (mg): 4		
	Mean %	Range	%CV	Mean %	Range	%CV
10	51.6		6.7	49.8		4.0
20	80.0		3.7	100.2		0.7
30	91.3		1.9	101.6		0.7
40	96.8		1.2	101.9		0.7
Sampling Times (Minutes)	Test Product LOT # D950810 Strength (mg): 5			Reference Product LOT # EHN306A Strength (mg): 5		
	Mean %	Range	%CV	Mean %	Range	%CV

10	56.1			5.3	50.2		7.5
20	85.6			2.8	88.2		6.5
30	95.7			1.3	98.5		2.2
40	99.3			0.7	98.7		2.2
Sampling Times (Minutes)	Test Product LOT # D950801 Strength (mg): 7.5			Reference Product LOT # EHK265A Strength (mg): 7.5			
	Mean %	Range	%CV	Mean %	Range	%CV	
10	64.6		4.9	57.9		5.0	
20	93.3		2.4	91.3		2.0	
30	100.8		1.3	100.2		1.4	
40	101.9		1.1	100.4		1.5	
Sampling Times (Minutes)	Test Product LOT# D950808 Strength (mg): 10			Reference Product LOT # EHB042A Strength (mg): 10			
	Mean %	Range	%CV	Mean %	Range	%CV	
10	66.2		3.9	57.8		6.1	
20	93.8		1.2	89.6		2.2	
30	100.2		0.6	100.9		1.0	
40	100.4		0.6	101.0		1.0	

VIII. Comments

1. Study under fasting conditions:

2 mg and 10 mg Warfarin Sodium Tablets (Invamed)

For 2 mg biostudy, 25 subjects completed two periods of study successfully, subject #11 withdrew, for reasons unrelated to study and his data were not included in the analysis. There were three missing samples.

For 10 mg biostudy, 24 subjects completed two periods of study successfully, subject #21 and #11 did not complete the study for reasons unrelated to study and their data were not included in the analysis.

The mean plasma levels for the test and reference products are comparable for both bio-studies. The test/reference ratios for the non-transformed and ln-transformed PK parameters range 0.96 to 1.0. The 90% confidence intervals for the ln-transformed AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} were all within the 80-125% range.

3. Waiver of bio-study for 1, 2.5, 4, 5, and 7.5 mg Strength:

The dissolution tests conducted by Invamed Pharmaceuticals, on its Warfarin Sodium 1, 2.5, 4, 5, and 7.5 mg tablets is acceptable. The formulation for the 1, 2.5, 4, 5, and 7.5

mg strength is proportionally similar to the 2 mg and 10 mg strength of the test product which underwent acceptable bioequivalence testing. Waiver of *in vivo* bioequivalence requirements is granted.

4. Assay validation:

Pre-study validation and within-study validation are acceptable.

5. Adverse events:

Under fasting conditions no clinically significant serious adverse reactions were reported for both bio-study. Thirty-six adverse events were reported in thirteen of twenty-six subjects dosed. Nature of events included bronchitis, conjunctivitis, cough, earache, eye abnormality, fatigue, headache, hypertonia, laceration, malaise, pain, pharyngitis, rhinitis and tonsillitis. There were no serious adverse events.

6. The batch size of test products was tablets of each strength.

7. Dissolution testing:

Firm has used USP method for dissolution and comparative data are acceptable for 1, 2, 2.5, 4, 5, 7.5 and 10 mg test tablets. Tolerance "Q" NLT dissolved in 30 minutes.

IX. Deficiency: None

X. Recommendation

1. The single-dose bioequivalence studies P95-242 and P95-243 conducted by Invamed, on its Warfarin Sodium 2 mg Tablets (lot #D950809) and 10 mg Tablets (lot#D950808) comparing it to Coumadin^R 2 mg Tablets (lot #EHJ245A) and 10 mg Tablets (lot#EHB042A), manufactured by DuPont-Merck, are found to be acceptable by the Division of Bioequivalence. The studies demonstrate that Invamed's 2 mg and 10 mg Warfarin Sodium Tablets are deemed bioequivalent to the reference product, Coumadin^R 2 mg and 10 mg Tablets, manufactured by DuPont-Merck.
2. The dissolution testing conducted by Invamed, on its 1 mg (lot#D950901), 2 mg (Lot #D950809), 2.5 mg (lot#D950806), 4 mg (lot#D950811), 5 mg (lot#D950810), 7.5 mg (lot#D950801), and 10 mg (Lot#D950808) Warfarin Sodium tablet is acceptable. The formulation for the 1, 2, 2.5, 4, 5, 7.5 mg strength are proportionally similar to the 2 mg and 10 mg test products which underwent acceptable bioequivalence testing. Waiver of *in vivo* bioequivalence study requirements for the 1, 2.5, 4, 5, and 7.5 mg tablet of the test product is granted. The Division of Bioequivalence deems Warfarin Sodium Tablet, 1, 2.5, 4, 5, and 7.5 mg, manufactured by Invamed to be bioequivalent to Coumadin^R Tablet, 1, 2.5, 4, 5, and 7.5 mg, manufactured by DuPont-Merck.
3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of deaerated water at 37°C using USP 23 apparatus 2 (paddle) at 50 RPM. The test drug should meet the following specifications:

Not less than of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

4. From the bioequivalence point of view, the firm has met the requirements of in vivo bioequivalence and in vitro dissolution testing and the application is approveable.

The firm should be informed of the recommendations.

12/24/96

A.P. Patel
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE .
FT INITIALED RMHATRE _____
Ramakant M. Mhatre, Ph.D.
Chief, Branch III
Division of Bioequivalence

Date: 11/13/96

Concur: _____

Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

Date: 11/18/96

cc: ANDA #40-196 (original, duplicate), HFD-658 (A.P. Patel), Drug File, Division File.